CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074381

Trade Name : DOBUTAMINE HCL INJECTION

Generic Name: Dobutamine Hcl Injection 12.5mg/ml

Sponsor : Elkins-Sinn

Approval Date: September 26, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074381

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074381

APPROVAL LETTER

ANDA 74-381

SEP 26 1996

Elkins-Sinn
Attention: Frances M. Cacchio
2 Esterbrook Lane
Cherry Hill, NJ 08003-4099

Dear Madam:

This is in reference to your abbreviated new drug application dated July 1, 1993, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Dobutamine Hydrochloride Injection, 12.5 mg (base)/mL.

Reference is also made to your amendments dated June 27, July 30, and September 13, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Dobutamine Hydrochloride for Injection USP, 12.5 mg/mL to be bioequivalent and, therefore, therapeutically equivalent to the listed drug Dobutrex® Solution 12.5 mg/mL of Eli Lilly and Company.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/ 9/26/96

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

DSG:a
9-24-96

cc: ANDA 74-381
ANDA 74-381/Division File
Field Copy
HFD-600/Reading File
HFD-8/P.Savino
HFD-610/J.Phillips

Endorsements:

HFD-623/JSmith/7-10-96
HFD-623/VSayeed/7-31-9
HFD-613/CPark/8-5-96
HFD-617/JWilson/8-16-9
HFD-613/AVezza/8-5-96
X:\NEW\FIRMSAM\ELKINS\
F/T by gp/8/16/96

/S/

CENTER FOR DRUG EVALUATION AND RESEARCH

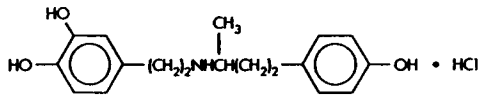
APPLICATION NUMBER 074381

FINAL PRINTED LABELING

J-2359B ESI ELKINS-SINN

DOBUTAMINE
HYDROCHLORIDE INJECTION

DESCRIPTION
Dobutamine Hydrochloride Injection is a synthetic catecholamine. The chemical name for dobutamine hydrochloride is (±)-4-[2-[[3-(*p*-Hydroxyphenyl)-1-methylpropyl]amino]ethyl]-pyrocatechol hydrochloride, and it has the following structural formula:



$C_{18}H_{23}NO_3 \cdot HCl$ MW 337.85

The clinical formulation is supplied in a sterile form for intravenous use only. Each mL contains dobutamine hydrochloride equivalent to 12.5 mg (41.5 μmol) dobutamine and sodium metabisulfite 0.24 mg in Water for Injection. Sodium hydroxide and/or hydrochloric acid added, if needed, for pH adjustment to pH 2.5-5.5.

CLINICAL PHARMACOLOGY
Dobutamine hydrochloride is a direct-acting inotropic agent whose primary activity results from stimulation of the β-receptors of the heart while producing comparatively mild chronotropic, hypertensive, arrhythmogenic and vasodilative effects. It does not cause the release of endogenous norepinephrine, as does dopamine. In animal studies, dobutamine produces less increase in heart rate and less decrease in peripheral vascular resistance for a given inotropic effect than does isoproterenol.

In patients with depressed cardiac function, both dobutamine and isoproterenol increase the cardiac output to a similar degree. In the case of dobutamine, this increase is usually not accompanied by marked increases in heart rate (although tachycardia is occasionally observed), and the cardiac stroke volume is usually increased. In contrast, isoproterenol increases the cardiac index primarily by increasing the heart rate while stroke volume changes little or declines.

Facilitation of atrioventricular conduction has been observed in human electrophysiologic studies and in patients with atrial fibrillation.

Systemic vascular resistance is usually decreased with administration of dobutamine. Occasionally, minimum vasoconstriction has been observed.

Most clinical experience with dobutamine is short-term—not more than several hours in duration. In the limited number of patients who were studied for 24, 48 and 72 hours, a persistent increase in cardiac output occurred in some, whereas output returned toward baseline values in others.

The onset of action of dobutamine is within 1 to 2 minutes; however, as much as 10 minutes may be required to obtain the peak effect of a particular infusion rate.

The plasma half-life of dobutamine in humans is 2 minutes. The principal routes of metabolism are methylation of the catechol and conjugation. In human urine, the major excretion products are the conjugates of dobutamine and 3-O-methyl dobutamine. The 3-O-methyl derivative of dobutamine is inactive.

Alteration of synaptic concentrations of catecholamines with either reserpine or tricyclic antidepressants does not alter the actions of dobutamine in animals, which indicates that the actions of dobutamine are not dependent on presynaptic mechanisms.

INDICATIONS AND USAGE
Dobutamine Hydrochloride Injection is indicated when parenteral therapy is necessary for inotropic support in the *short-term* treatment of adults with cardiac decompensation due to depressed contractility resulting either from organic heart disease or from cardiac surgical procedures.

In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior to institution of therapy with dobutamine hydrochloride.

CONTRAINDICATIONS
Dobutamine hydrochloride is contraindicated in patients with idiopathic hypertrophic subaortic stenosis and in patients who have shown previous manifestations of hypersensitivity to Dobutamine Hydrochloride Injection.

WARNINGS
1. **INCREASE IN HEART RATE OR BLOOD PRESSURE**
   Dobutamine may cause a marked increase in heart rate or blood pressure, especially systolic pressure. Approximately 10% of patients in clinical studies have had rate increases of 30 beats/minute or more, and about 7.5% have had a 50-mm Hg or greater increase in systolic pressure. Usually, reduction of dosage promptly reverses these effects. Because dobutamine facilitates atrioventricular conduction, patients with atrial fibrillation are at risk of developing rapid ventricular response. Patients with preexisting hypertension appear to face an increased risk of developing an exaggerated pressor response.
2. **ECTOPIC ACTIVITY**
   Dobutamine may precipitate or exacerbate ventricular ectopic activity, but it rarely has caused ventricular tachycardia.
3. **HYPERSENSITIVITY**
   Reactions suggestive of hypersensitivity associated with administration of Dobutamine Hydrochloride Injection, including skin rash, fever, eosinophilia and bronchospasm, have been reported occasionally.
4. Dobutamine Hydrochloride Injection contains sodium metabisulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes, in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

PRECAUTIONS
GENERAL
1. **During the administration of Dobutamine Hydrochloride Injection, as with any adrenergic agent, ECG and blood pressure should be continuously monitored. In addition, pulmonary wedge pressure and cardiac output should be monitored whenever possible to aid in the safe and effective infusion of Dobutamine Hydrochloride Injection.**
2. Hypovolemia should be corrected with suitable volume expanders before treatment with dobutamine is instituted.
3. No improvement may be observed in the presence of marked mechanical obstruction, such as severe valvular aortic stenosis.

USAGE FOLLOWING ACUTE MYOCARDIAL INFARCTION
Clinical experience with Dobutamine Hydrochloride Injection following myocardial infarction has been insufficient to establish the safety of the drug for this use. There is concern that any agent that increases contractile force and heart rate may increase the size of an infarction by intensifying ischemia, but it is not known whether dobutamine does so.

LABORATORY TESTS
Dobutamine, like other β_2-agonists, can produce a mild reduction in serum potassium concentration, rarely to hypokalemic levels. Accordingly, consideration should be given to monitoring serum potassium.

DRUG INTERACTIONS
Animal studies indicate that dobutamine may be ineffective if the patient has recently received a β-blocking drug. In such a case, the peripheral vascular resistance may increase.

Preliminary studies indicate that the concomitant use of dobutamine and nitroprusside results in a higher cardiac output and, usually, a lower pulmonary wedge pressure than when either drug is used alone.

There was no evidence of drug interactions in clinical studies in which dobutamine was administered concurrently with other drugs, including digitalis preparations, furosemide, spironolactone, lidocaine, nitroglycerin, isosorbide dinitrate, morphine, atropine, heparin, protamine, potassium chloride, folic acid and acetaminophen.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY
Studies to evaluate the carcinogenic or mutagenic potential of dobutamine, or its potential to affect fertility, have not been conducted.

PREGNANCY
Teratogenic Effects—Pregnancy Category B. Reproduction studies performed in rats at doses up to the normal

1. During the administration of Dobutamine Hydrochloride Injection, **blood pressure should be continuously monitored. In addition, pulmonary wedge pressure and cardiac output should be monitored whenever possible to aid in the safe and effective infusion of Dobutamine Hydrochloride Injection.**
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CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Studies to evaluate the carcinogenic or mutagenic potential of dobutamine, or its potential to affect fertility, have not been conducted.

PREGNANCY

Teratogenic Effects—Pregnancy Category B. Reproduction studies performed in rats at doses up to the normal human dose (10 mcg/kg/min for 24 h, total daily dose of 14.4 mg/kg) and in rabbits at doses up to twice the normal human dose have revealed no evidence of harm to the fetus due to dobutamine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

LABOR AND DELIVERY

The effect of Dobutamine Hydrochloride Injection on labor and delivery is unknown.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when dobutamine hydrochloride is administered to a nursing woman. If a mother requires dobutamine treatment, breast-feeding should be discontinued for the duration of the treatment.

PEDIATRIC USE

The safety and effectiveness of Dobutamine Hydrochloride Injection for use in pediatric patients have not been studied.

ADVERSE REACTIONS

INCREASED HEART RATE, BLOOD PRESSURE AND VENTRICULAR ECTOPIC ACTIVITY

A 10- to 20-mm increase in systolic blood pressure and an increase in heart rate of 5 to 15 beats/minute have been noted in most patients (see WARNINGS regarding exaggerated chronotropic and pressor effects). Approximately 5% of patients have had increased premature ventricular beats during infusions. These effects are dose related.

HYPOTENSION

Precipitous decreases in blood pressure have occasionally been described in association with dobutamine therapy. Decreasing the dose or discontinuing the infusion typically results in rapid return of blood pressure to baseline values. In rare cases, however, intervention may be required and reversibility may not be immediate.

REACTIONS AT SITES OF INTRAVENOUS INFUSION

Phlebitis has occasionally been reported. Local inflammatory changes have been described following inadvertent infiltration. Isolated cases of cutaneous necrosis (destruction of skin tissue) have been reported.

MISCELLANEOUS UNCOMMON EFFECTS

The following adverse effects have been reported in 1% to 3% of patients: nausea, headache, anginal pain, nonspecific chest pain, palpitations and shortness of breath.

Isolated cases of thrombocytopenia have been reported.

Administration of dobutamine, like other catecholamines, can produce a mild reduction in serum potassium concentration, rarely to hypokalemic levels (see PRECAUTIONS).

LONGER-TERM SAFETY

Infusions of up to 72 hours have revealed no adverse effects other than those seen with shorter infusions.

OVERDOSAGE

Overdoses of dobutamine have been reported rarely. The following is provided to serve as a guide if such an overdose is encountered.

SIGNS AND SYMPTOMS

Toxicity from dobutamine hydrochloride is usually due to excessive cardiac β-receptor stimulation. The duration of action of dobutamine hydrochloride is generally short ($T_{1/2}$ = 2 minutes) because it is rapidly metabolized by catechol-O-methyltransferase. The symptoms of toxicity may include anorexia, nausea, vomiting, tremor, anxiety, palpitations, headache, shortness of breath and anginal and nonspecific chest pain. The positive inotropic and chronotropic effects of dobutamine on the myocardium may cause hypertension, tachyarrhythmias, myocardial ischemia and ventricular fibrillation. Hypotension may result from vasodilation.

TREATMENT

To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*. In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs and unusual drug kinetics in your patient.

The initial actions to be taken in a dobutamine hydrochloride overdose are discontinuing administration, establishing an airway and ensuring oxygenation and ventilation. Resuscitative measures should be initiated promptly. Severe ventricular tachyarrhythmias may be successfully treated with propranolol or lidocaine. Hypertension usually responds to a reduction in dose or discontinuation of therapy.

Protect the patient's airway and support ventilation and perfusion. If needed, meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc.

If the product is ingested, unpredictable absorption may occur from the mouth and the gastrointestinal tract. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

Forced diuresis, peritoneal dialysis, hemodialysis or charcoal hemoperfusion have not been established as beneficial for an overdose of dobutamine hydrochloride.

DOSAGE AND ADMINISTRATION

NOTE: Do not add Dobutamine Hydrochloride Injection to 5% Sodium Bicarbonate Injection or to any other strongly alkaline solution. Because of potential physical incompatibilities, it is recommended that dobutamine hydrochloride not be mixed with other drugs in the same solution. Dobutamine hydrochloride should not be used in conjunction with other agents or diluents containing both sodium metabisulfite and ethanol.

PREPARATION AND STABILITY

At the time of administration, Dobutamine Hydrochloride Injection must be further diluted in an IV container to at least a 50 mL solution using one of the following intravenous solutions as a diluent: Dextrose Injection 5%, Dextrose 5% and Sodium Chloride 0.45% Injection, Dextrose 5% and Sodium Chloride 0.9% Injection, Dextrose Injection 10%, Isolyte® M with Dextrose 5% Injection, Lactated Ringer's Injection, Dextrose 5% in Lactated Ringer's Injection, Normosol®-M in D5-W, Osmitrol® 20% in Water for Injection, Sodium Chloride Injection 0.9% or Sodium Lactate Injection. Intravenous solutions should be used within 24 hours.

RECOMMENDED DOSAGE

The rate of infusion needed to increase cardiac output usually ranged from 2.5 to 15 mcg/kg/min (see Table 1). On rare occasions, infusion rates up to 40 mcg/kg/min have been required to obtain the desired effect.

TABLE 1
Dobutamine Hydrochloride Injection Infusion Rate (mL/kg/min) for Concentrations of 250, 500 and 1000 mcg/mL

Drug Delivery Rate (mcg/kg/min)	Infusion Delivery Rate: 250 mcg/mL* (mL/kg/min)	500 mcg/mL† (mL/kg/min)	1000 mcg/mL‡ (mL/kg/min)
2.5	0.01	0.005	0.0025
5	0.02	0.01	0.005
7.5	0.03	0.015	0.0075
10	0.04	0.02	0.01
12.5	0.05	0.025	0.0125
15	0.06	0.03	0.015

* 250 mcg/mL of diluent
† 500 mcg/mL or 250 mg/500 mL of diluent
‡ 1000 mcg/mL or 250 mg/250 mL of diluent

Rates of infusion in mL/h for Dobutamine Hydrochloride Injection concentrations of 500 mcg/mL, 1000 mcg/mL and 2000 mcg/mL are given in Table 2.

TABLE 2
Dobutamine Hydrochloride Injection Infusion Rate (mL/h) for 500 mcg/mL Concentration

Drug Delivery Rate (mcg/kg/min)	Patient Body Weight (kg): 30	40	50	60	70	80	90	100	110
2.5	9	12	15	18	21	24	27	30	33
5	18	24	30	36	42	48	54	60	66
7.5	27	36	45	54	63	72	81	90	99
10	36	48	60	72	84	96	108	120	132
12.5	45	60	75	90	105	120	135	150	165
15	54	72	90	108	126	144	162	180	198

Dobutamine Hydrochloride Injection Infusion Rate (mL/h) for 1000 mcg/mL Concentration

Drug Delivery Rate (mcg/kg/min)	Patient Body Weight (kg): 30	40	50	60	70	80	90	100	110
2.5	4.5	6	7.5	9	10.5	12	13.5	15	16.5
5	9	12	15	18	21	24	27	30	33
7.5	13.5	18	22.5	27	31.5	36	40.5	45	49.5
10	18	24	30	36	42	48	54	60	66
12.5	22.5	30	37.5	45	52.5	60	67.5	75	82.5
15	27	36	45	54	63	72	81	90	99

Dobutamine Hydrochloride Injection Infusion Rate (mL/h) for 2000 mcg/mL Concentration

Drug Delivery Rate (mcg/kg/min)	Patient Body Weight (kg): 30	40	50	60	70	80	90	100	110
2.5	2	3	4	4.5	5	6	7	7.5	8
5	4.5	6	7.5	9	10.5	12	13.5	15	16.5
7.5	7	9	11	13.5	16	18	20	22.5	25
10	9	12	15	18	21	24	27	30	33
12.5	11	15	19	22.5	26	30	34	37.5	41
15	13.5	18	22.5	27	31.5	36	40.5	45	49.5

The rate of administration and the duration of therapy should be adjusted according to the patient's response as determined by heart rate, presence of ectopic activity, blood pressure, urine flow and, whenever possible, measurement of central venous or pulmonary wedge pressure and cardiac output.

Concentrations of up to 5000 mcg/mL have been administered to humans (250 mg/50 mL). The final volume administered should be determined by the fluid requirements of the patient.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

HOW SUPPLIED

Dobutamine Hydrochloride Injection equivalent to 12.5 mg dobutamine per mL is available in the following:

20 mL (250 mg) *SINGLE DOSE* vial packaged in 25s (*NDC* 0641-2359-45)

STORAGE

Store at controlled room temperature 15°-30°C (59°-86°F).

Caution: Federal law prohibits dispensing without prescription.

* * * * *

Issued April 1996
J-2359B

Manufactured by
ELKINS-SINN, Cherry Hill, NJ 08003-4099
A division of A. H. Robins Company

DOBUTAMINE HYDROCHLORIDE

Attach this label to the IV infusion bottle. I-2359

Patient's name _____

Total volume _____

Total number of mg added to bag _____

Dose : μg/kg/min _____

Rate of infusion : mL/min _____ OR

SEP 26 1996 microdrops/min _____

Date _____ Time _____

Prepared by _____

ESI ELKINS-SINN, Cherry Hill, NJ 08003-4099

---

20 mL *SINGLE DOSE* Vial
NDC 0641-2359-41

DOBUTAMINE
HYDROCHLORIDE INJECTION
250 mg/20 mL
equiv. to 12.5 mg/mL of dobutamine
FOR IV USE ONLY
MUST BE DILUTED PRIOR TO USE

ESI ELKINS-SINN, Cherry Hill, NJ 08003-4099

CONTAINS NO ANTIMICROBIAL PRESERVATIVES. Each mL contains dobutamine hydrochloride (equivalent to 12.5 mg dobutamine) and 0.24 mg sodium metabisulfite in Water for Injection. pH 2.5-5.5; sodium hydroxide and/or hydrochloric acid added, if needed, for pH adjustment. Caution: Federal law prohibits dispensing without prescription.

SINGLE DOSE VIAL DISCARD UNUSED CONTENTS USE WITHIN 24 HOURS AFTER DILUTION

USUAL DOSAGE: See package insert for complete prescribing information and IV dilution. Store at controlled room temperature 15°-30°C (59°-86°F). Product Code: 2359-41 A-2359

LOT EXP.

1996

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10 X 20 mL *SINGLE DOSE* Vials *NDC* 0641-2359-43

DOBUTAMINE
HYDROCHLORIDE INJECTION
250 mg/20 mL
equiv. to 12.5 mg/mL of dobutamine
FOR IV USE ONLY
MUST BE DILUTED PRIOR TO USE

ESI ELKINS-SINN, Cherry Hill, NJ 08003-4099
A division of A. H. Robins Company

CONTAINS NO ANTIMICROBIAL PRESERVATIVES. SINGLE DOSE VIAL — DISCARD UNUSED CONTENTS. USE WITHIN 24 HOURS AFTER DILUTION. Each mL contains dobutamine hydrochloride (equivalent to 12.5 mg dobutamine) and 0.24 mg sodium metabisulfite in Water for Injection. pH 2.5-5.5; sodium hydroxide and/or hydrochloric acid added, if needed, for pH adjustment. **USUAL DOSAGE:** See package insert for complete prescribing information and IV dilution. Store at controlled room temperature 15°-30°C (59°-86°F).
Caution: Federal law prohibits dispensing without prescription. Product Code: 2359-43 B-32359

LOT EXP.

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25 X 20 mL *SINGLE DOSE* Vials *NDC* 0641-2359-45

DOBUTAMINE
HYDROCHLORIDE INJECTION
250 mg/20 mL
equiv. to 12.5 mg/mL of dobutamine
FOR IV USE ONLY
MUST BE DILUTED PRIOR TO USE

ESI ELKINS-SINN, Cherry Hill, NJ 08003-4099
A division of A. H. Robins Company

CONTAINS NO ANTIMICROBIAL PRESERVATIVES. SINGLE DOSE VIAL — DISCARD UNUSED CONTENTS. USE WITHIN 24 HOURS AFTER DILUTION. Each mL contains dobutamine hydrochloride (equivalent to 12.5 mg dobutamine) and 0.24 mg sodium metabisulfite in Water for Injection. pH 2.5-5.5; sodium hydroxide and/or hydrochloric acid added, if needed, for pH adjustment. **USUAL DOSAGE:** See package insert for complete prescribing information and IV dilution. Store at controlled room temperature 15°-30°C (59°-86°F).
Caution: Federal law prohibits dispensing without prescription. Product Code: 2359-45 B-32359

LOT EXP.

26 1996

DOBUTAMINE
HCl INJECTION
250 mg/20 mL

DOBUTAMINE
HCl INJECTION
250 mg/20 mL
equivalent to 12.5 mg/mL of dobutamine
FOR IV USE ONLY

MUST BE DILUTED PRIOR TO USE

CONTAINS NO ANTIMICROBIAL PRESERVATIVES

Each mL contains dobutamine hydrochloride (equivalent to 12.5 mg dobutamine) and 0.24 mg sodium metabisulfite in Water for Injection. pH 2.5-5.5; sodium hydroxide and/or hydrochloric acid added, if needed, for pH adjustment.

Caution: Federal law prohibits dispensing without prescription.

esi

20 mL *SINGLE DOSE* Vial
NDC 0641-2359-41
6505-01-239-4660

DOBUTAMINE
HCl INJECTION
250 mg/20 mL
equivalent to 12.5 mg/mL of dobutamine
FOR IV USE ONLY

MUST BE DILUTED PRIOR TO USE

SINGLE DOSE VIAL
DISCARD UNUSED CONTENTS
USE WITHIN 24 HOURS AFTER DILUTION

USUAL DOSAGE
See package insert for complete prescribing information and IV dilution.

STORAGE
Store at controlled room temperature 15°-30°C (59°-86°F).

Product Code
2359-41 B-12359

esi **ELKINS-SINN**
Cherry Hill, NJ 08003
A division of A. H. Robins Co. esi

SEP 26 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074381

CHEMISTRY REVIEW(S)

Addendum to the Chemistry Review

ANDA 74-381 **Elkins-Sinn**

Dobutamine Hydrochloride Injection, 12.5 mg (base)/mL

Addendum Items:

1. Methods validation telephone amendment:

   Because of a delay in submitting the methods validation package to a district laboratory, OGD was considering approving the application before methods validation was complete.

   In order to facilitate this, the firm committed in the telephone amendment dated September 13, 1996 to "...work with the District Laboratory to resolve any questions which are raised related to..." methods validation by the District Laboratory.

   However, this amendment is irrelevant. A telephone call with Diane O'Brien at the Baltimore Lab (410-962-3791 Ext.148) on September 24, 1996 provided word that the methods validation has been completed. No problems were found and the lab will be recommending approval when the paperwork comes through.

2. Labeling:

   Labeling was pending at the time of the original chemistry review. All labeling issues have since been resolved.

3. Preapproval summary:

   The preapproval summary states that the drug product is compendial. This is incorrect since the official position of OGD is that there is no USP monograph for Dobutamine HCl Injection. As noted above, a methods validation package was submitted for evaluation.

Reviewer: John Smith Date of Addendum: September 24, 1996

/S/

1. CHEMISTRY REVIEW NO. 5

2. ANDA 74-381

3. NAME AND ADDRESS OF APPLICANT
Elkins-Sinn
Attention: Frances M. Cacchio
2 Esterbrook Lane
Cherry Hill, NJ 08003-4099

6. PROPRIETARY NAME
NA

7. NONPROPRIETARY NAME
Dobutamine Hydrochloride
Injection

10. PHARMACOLOGICAL CATEGORY
cardiac decompensation

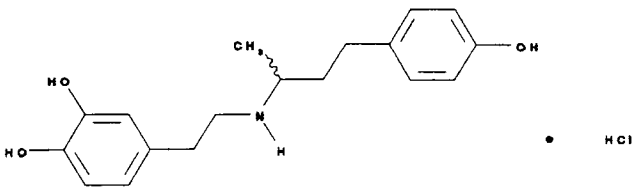
11. Rx

13. DOSAGE FORM
parenteral for IV infusion

14. POTENCY
12.5 mg (base)/mL, mL vial

15. CHEMICAL NAME AND STRUCTURE

(±)-4-[2-[[3-(*p*-Hydroxyphenyl)-1-methylpropyl]amino]ethyl] pyrocatechol hydrochloride



$C_{18}H_{23}NO_3.HCl$ CAS [49745-95-1] M.W. = 337.85

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend: APPROVAL.

19. REVIEWER: J. Smith

DATE COMPLETED: 07/10/96

Labeling OK as of 7/24/96
8/24/96

cc: ANDA 74-381
Division File
DUP Jacket
Field Copy

Endorsements:
HFD-623/J.Smith/7/10/96
HFD-623/V.Sayeed/7/31/9
/S/
X:\NEW\FIRMSAM\ELKINS\L
F/T by: gp/8/16/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074381

BIOEQUIVALENCE REVIEW(S)

OCT 28 1993

Dobutamine Hydrochloride Injection
12.5 mg/mL
ANDA #74-381
Reviewer: Z.Z. Wahba
File name: 74381W.793

Elkins-Sinn Pharmaceuticals
Cherry Hill, NJ
Submission Date:
July 01, 1993

REVIEW OF A WAIVER REQUEST

The firm has requested a waiver of in vivo bioavailability study requirements for its drug product, Dobutamine Hydrochloride Injection, USP, 12.5 mg/mL in 20 mL vials. The reference product is Dobutrex^{R}, manufactured by Eli Lilly.

FORMULATION COMPARISON

Ingredients	Test Product mg/mL	Ref Product mg/mL
Dobutamine HCl, USP (as base)	14.01*	12.5
Sodium Metabisulfite, NF	0.24	--
Sodium Bisulfite	--	0.24
0.1 N NaOH or HCl for	pH adjust.	pH adjust.
Water for Injection, USP	qs	qs
Nitrogen, NF	--	--

* 14.01 mg salt = 12.5 mg base

COMMENTS

1. The test drug product is an aqueous injectable solution for IV infusion.

2. The test and reference products contain the same amount (12.5 mg base/mL) of the active ingredient. However, the test product contains sodium metabisulfite instead of sodium bisulfite which is used in the reference product. The monograph of sodium bisulfite of NF XV reads "Note-Where Sodium Bisulfite is called for, use Sodium Metabisulfite". The monograph of sodium bisulfite was deleted from NF XVII.

3. The waiver of in vivo bioequivalence study requirements should be granted based on 21 CFR section 320.22(b)(1) of the Bioavailability/Bioequivalence Regulations.

RECOMMENDATION

The Division of Bioequivalence agrees that the information submitted by Elkins-Sinn Pharmaceuticals demonstrates that Dobutamine Hydrochloride Injection, USP, 12.5 mg/mL packaged in 20 mL vials falls under 21 CFR Section 320.22(b)(1) of the Bioavailability/Bioequivalence Regulations. The waiver of in vivo bioequivalence study for the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test product to be bioequivalent to Dobutrex^{R} Injection, 12.5 mg/mL packaged in 20 mL vials manufactured by Eli Lilly.

The firm should be informed of the recommendation.

/S/

Zakaria Z. Wahba, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE

/S/ 10/28/93

cc: ANDA #74-381 (original, duplicate), HFD-600 (Hare), HFD-630, HFC-130 (JAllen), HFD-658 (Mhatre, Wahba), Drug File, Division File
ZZWahba/093093